Current Research Studies on Multicultural Aspects of Breast Cancer Etiology

Prepared for the Workshop on Multicultural Aspects of Breast Cancer Etiology

March 17-19, 1999
Washington, DC

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CURRENT RESEARCH STUDIES ON MULTICULTURAL ASPECTS OF BREAST CANCER ETIOLOGY

March 1999
Prepared by R.O.W. Sciences, Inc., for the
National Action Plan on Breast Cancer
Etiology Working Group

This report was prepared for the Etiology Working Group of the National Action Plan on Breast Cancer (NAPBC) by R.O.W. Sciences, Inc., under the direction of the U.S. Public Health Service's Office on Women's Health (PHS OWH) and the Planning Committee for the Workshop on Multicultural Aspects of Breast Cancer Etiology. The editorial contents of this document represent the ideas and opinions of the principal investigators who supplied the information and do not necessarily reflect those of PHS OWH, the NAPBC, or the Planning Committee.

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CURRENT RESEARCH STUDIES ON MULTICULTURAL ASPECTS OF BREAST CANCER ETIOLOGY

INTRODUCTION

As part of its charge to expand the scope of biomedical research in the areas of lifestyle factors, environmental conditions, genetic predispositions, etiologic aspects of breast cancer tumor biology, and epidemiologic study design, the Etiology Working Group of the National Action Plan on Breast Cancer (NAPBC) recognizes the particular importance and uniquely complicated nature of multicultural aspects of breast cancer etiology.

Purpose of the Report

This document was prepared in conjunction with the Workshop on Multicultural Aspects of Breast Cancer Etiology, convened by the Etiology Working Group on March 17 through 19, 1999, in Washington, DC. The purpose of the document is to assist the Working Group in identifying gaps in research by describing etiologic, multicultural studies that currently are being conducted or recently have been completed and, therefore, are not reflected in published literature. This report is one of three documents facilitating the workshop planning committee's effort to examine research in this area, identify gaps in the research, and promote liaisons, both for the workshop and for future Etiology Working Group activities. The other two documents are a literature review (*Multicultural Aspects of Breast Cancer Etiology: A Review of the Literature*) and a bibliography (*Current Bibliographies in Medicine: Multicultural Aspects of Breast Cancer Etiology*).

Selection Criteria

To produce a document that corresponds to the needs of the Etiology Working Group and is appropriate in size, scope, and cost, criteria were identified for selecting the abstracts to be included. Abstracts were included only for current research studies; abstracts that describe service projects or data collection projects that serve as tools or resources for future studies were not included. The studies that were included:

- Address etiologic issues;
- Address multicultural issues;
- Are ongoing (i.e., are not completed and have not been described previously in published literature. However, the Etiology Working Group decided to include studies that were completed at or since the end of 1998 if the results had not been published.);
- Address populations identified in the *Office of Management and Budget Statistical Directive 15* (for consistency with the literature review that accompanies this document and with the workshop agenda); and

- Were approved for inclusion by their principal investigators (PIs).

Several studies and programs on which information was collected could not be included because they did not satisfy the criteria (e.g., they focused on screening or survival; the descriptions were not approved by the PIs). However, the bibliography developed in conjunction with this document is broader in scope and contains information on some of these topics and others not addressed here.

Process Used for Identifying and Selecting Studies

1. Studies were identified initially using two methods:

    - Conducting searches of the Computer Retrieval of Information on Scientific Projects (CRISP), the Physician Data Query (PDQ), and the Office of Minority Health databases, as well as reviewing the Federal Coordinating Committee on Breast Cancer's 1997 Summary of Funded Projects and the National Cancer Institute's Portfolio Analysis.

    - Conducting telephone interviews with researchers and advocates in the field of breast cancer, including members of the Etiology Working Group, the Planning Committee for the Workshop on Multicultural Aspects of Breast Cancer Etiology, the Intercultural Cancer Council, and representatives of major funding sources and research facilities.

2. The PIs were contacted to obtain more information on the studies that appeared to satisfy the selection criteria.

3. For each study, a description was prepared that included an abstract obtained from the PI or, in cases where an abstract was not available, an abstract that was drafted based on telephone interviews. The descriptions were sent to the PIs, who were asked to review them, make changes if necessary, and return them with permission to include them in the document.

Organization of the Report

The studies included in this report are organized alphabetically by funding source; within each funding source, they are organized alphabetically by institution. The matrix that is included in the front of the report provides an overview of the information detailed in the report, specifically, the risk factors and races/ethnicities examined in each study.*

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* For the purpose of consistency, the categories of races and ethnicities used in the matrix and the majority used in the study descriptions parallel those specified in the *Office of Management and Budget Statistical Directive 15*. However, several studies' descriptions use the categories cited by the authors.

Acronyms

Following is a list of frequently used acronyms for funding organizations and programs:

ACS	American Cancer Society
CDC	Centers for Disease Control and Prevention
DoD	Department of Defense
MBRS	Minority Biomedical Research Support
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NHLBI	National Heart, Lung, and Blood Institute
NIOSH	National Institute for Occupational Safety and Health
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
USAMRMC	U.S. Army Medical Research and Materiel Command

Additional frequently used acronyms are listed below:

BMD	bone mineral density
CBCS	Carolina Breast Cancer Study
ER	estrogen receptor
PCR	polymerase chain reaction
PR	progesterone receptor
WHI	Women's Health Initiative
SPORE	Specialized Program of Research Excellence in Breast Cancer

Matrix of Current Studies on

Multicultural Aspects of Breast Cancer Etiology

Matrix of Current Research Studies on Multicultural Aspects of Breast Cancer Etiology

FUNDING SOURCE TITLE OF STUDY* (PI/CONTACT)	SUBJECT AREA/RISK FACTOR										RACE/ETHNICITY						
	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
1. AMERICAN CANCER SOCIETY																	
ACS CPS-II Database (Calle)										•	•	•	•	•	•	•	
2. CALIFORNIA BREAST CANCER RESEARCH PROGRAM																	
A Case-Control Study of Breast Cancer in Asian Americans (Wu)	•		•					•					•				
Gene-Diet/Tobacco Interactions in Breast Cancer in Asians (Wu)		•	•	•						•			•				
3. CENTERS FOR DISEASE CONTROL AND PREVENTION/NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH																	
Biomarkers of Occupational Disease Risk: Role in Human Carcinogenesis (Ecogenics of Breast Cancer) (Weston)		•		•							•			•	•		
Effect of Exposure to Acetaminophen and Chemicals on Breast Cancer (Castranova, Huffman, Miller)		•			•												•
4. DEPARTMENT OF DEFENSE																	
Novel Recruitment Techniques (Ambrosone)			•							•	•						

* Some of the titles are abbreviated.

** "Other Risk Factors" are factors that are not addressed in the other subject area/risk factor categories and factors that are unspecified in the research descriptions.

*** "Other Groups" are groups that are not addressed in the other race/ethnicity categories and groups that are unspecified in the research descriptions.

Matrix of Current Research Studies on Multicultural Aspects of Breast Cancer Etiology (continued)

FUNDING SOURCE TITLE OF STUDY* (PI/CONTACT)	SUBJECT AREA/RISK FACTOR										RACE/ETHNICITY						
	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
Diet, Genetic Polymorphisms, and Breast Cancer in African Americans (Adams-Campbell)			•	•							•						
Relationship Between Endocrine Factors and Breast Cancer Risk (Agurs-Collins)	•				•			•		•	•						
BRCA1 and BRCA2 Mutations in African Americans (Broome)				•							•						
ER in Breast Cancer (Poola)					•						•						
Methyl-Deficient Diets and Risk of Breast Cancer (Zhu)			•	•							•						
Racial/Ethnic Differences in Breast Cancer Risk Factors (John)	•		•		•			•	•	•	•			•	•		
Ethnicity, Soy Bean Consumption, and Mammographic Density Patterns (Maskarinec)			•			•							•	•		•	
5. NATIONAL INSTITUTES OF HEALTH/NATIONAL CANCER INSTITUTE																	
Case-Control Study of DMPA and Breast Cancer (Shapiro, Rosenberg)					•				•		•						•

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Matrix of Current Research Studies on Multicultural Aspects of Breast Cancer Etiology (continued)

FUNDING SOURCE TITLE OF STUDY* (PI/CONTACT)	SUBJECT AREA/RISK FACTOR										RACE/ETHNICITY						
	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
Followup Study for Causes of Illness in Black Women (Rosenberg, Palmer, Adams-Campbell)		•	•		•			•	•	•	•						
Case-Control Surveillance Study of Medications and Cancer (Rosenberg, Palmer, Shapiro, Strom)										•							•
Benign Breast Disease: Molecular Differentiation of Risk (Worsham)				•			•				•			•			•
Plasma IGF-1 and IGFBP3 in Minority Breast Cancer Patients (Vadgama)							•										•
Racial Differences in Breast Cancer Survival (Flagg)	•			•	•		•				•			•			
Inherited Breast Cancer in Chinese Women (Ostrander)				•									•				
Gene Regulation in Breast, Colon, and Skin Cancer (Day)				•							•			•	•		
Risk Factors for Breast Cancer Among Women in China (Li)			•						•	•			•				•
Breast Cancer and Risk Factors Among African American Women: ER Status (Zhu)				•	•						•						

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	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
Breast Cancer in Women of Polish Ancestry (Pathak)		•	•		•				•	•				•			•
Genetic Mutations in Malignancy (Lyn)				•							•						
Prevalence of BRCA1: A Population-Based Study (Bernstein)				•							•			•			
Molecular Epidemiology of Breast Cancer (Bernstein)				•													•
Environmental and Genetic Determinants of Breast Cancer (Wolff)		•	•	•					•								•
Breast Cancer Risk Factors in Hispanic Women (John)			•					•	•	•					•		
Multiethnic/Minority Cohort Study of Diet and Cancer (Kolonel)			•								•		•	•	•	•	
Defining Diet-Related Breast Cancer Risks in Black Women (Kumanyika)			•							•	•						
HEAL Study in Breast Cancer Prognosis Among Black, Hispanic, and Non-Hispanic White Women (Ballard-Barbash)	•		•	•	•		•	•			•			•	•		
SPORE in Breast Cancer (Earp)				•						•	•			•			

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	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
SPORE in Breast Cancer: Carolina Breast Cancer Study (Newman)		•		•	•		•			•	•			•			
SPORE in Breast Cancer: Case-Control Study of Carcinoma in Situ (Millikan)		•		•			•			•	•			•			
Genetic Differences in H-ras VNTR between Races (Conway-Dorsey)				•							•			•			
Genotype/Hormone Interactions in Breast Cancer Susceptibility (Rebbeck)				•	•		•		•		•			•			
Activity of P450-1A2 and 3A4 and Breast Cancer Risk (Zheng)					•					•			•				
BRCA1 and BRCA2 in African American and Latino Families (Henderson)				•						•	•				•		
Breast Cancer Risk Factors of Hispanic and Non-Hispanic White Women (Gilliland)	•		•					•	•	•				•	•		
Medication Use and Breast Cancer (Moorman)					•				•	•	•			•			

* Some of the titles are abbreviated.

** "Other Risk Factors" are factors that are not addressed in the other subject area/risk factor categories and factors that are unspecified in the research descriptions.

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6. NATIONAL INSTITUTES OF HEALTH/NATIONAL HEART, LUNG, AND BLOOD INSTITUTE																	
The Women's Health Initiative (Rossouw, Hurd)			•		•		•		•	•	•	•	•	•	•	•	
7. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES																	
Ethnicity, Body Composition, Bone Density, and Breast Cancer (Chen)	•									•					•		
8. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT																	
Women's CARE Study (Spirtas)				•	•		•				•			•			
9. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES																	
See Environmental and Genetic Determinants of Breast Cancer (Wolff) under NCI																	
10. NORTH CENTRAL CANCER TREATMENT GROUP																	
Breast Cancer Risk Factors and Mammographic Breast Density (Kaur, Roubidoux)						•				•		•					

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** "Other Risk Factors" are factors that are not addressed in the other subject area/risk factor categories and factors that are unspecified in the research descriptions.
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Matrix of Current Research Studies on Multicultural Aspects of Breast Cancer Etiology (continued)

FUNDING SOURCE TITLE OF STUDY* (PI/CONTACT)	SUBJECT AREA/RISK FACTOR										RACE/ETHNICITY						
	Anthropometric	Chemical	Diet/Nutrition	Genetic	Hormones	Mammographic	Pathology/Histology	Physical Activity	Reproductive	Other Risk Factors**	African American/Black	American Indian/Alaska Native	Asian	White	Hispanic	Native Hawaiian/Other Pacific Islander	Other Groups***
Molecular Markers in American Indian and Alaska Native Women with Breast Cancer (Kaur)				•								•		•			
11. SUSAN G. KOMEN BREAST CANCER FOUNDATION																	
Visceral Fat, BMD, and Breast Cancer: African Americans (Adams-Campbell)	•				•						•						
Establishing Tumor Tissue Banks and DNA and cDNA Gene Banks (Poola)			•	•	•		•			•	•						
Clinical and Genetic Screening of High-Risk African American Breast Cancer Families (McKetty)				•		•	•				•						

* Some of the titles are abbreviated.

** "Other Risk Faetors" are factors that are not addressed in the other subjeet area/risk factor catcgorics and factors that are unspeeifiecl in the research descriptions.

*** "Other Groups" are groups that are not addressed in the other race/ethnieity categories and groups that are unspeeifiecl in the research deseriptions.

DESCRIPTIONS OF CURRENT STUDIES

1. AMERICAN CANCER SOCIETY

ACS CPS-II Database

Institution: American Cancer Society
Study Start Date: 1982
Study End Date: N/A
Principal Investigator/Contact: Eugenia I. Calle, Ph.D.

Department of Epidemiology and Surveillance Research
American Cancer Society
1599 Clifton Road, NE
Atlanta, GA 30329
404-329-5741
404-321-4669 (fax)

The ACS Cancer Prevention Study-II (CPS-II) is a prospective mortality study of approximately 1.2 million American men and women of all races and ethnicities. Participants were recruited in 1982 and completed a questionnaire about demographic, behavioral, lifestyle, and disease characteristics. Approximately 52,000 study participants are African American. Each participant's vital status is determined at 2-year intervals through linkage with the National Death Index. Mortality followup is currently complete through 1996. Dr. Calle estimates that in 2 years, ACS will complete a report on risk factors associated with breast cancer mortality in African American women.

2. CALIFORNIA BREAST CANCER RESEARCH PROGRAM

A Case-Control Study of Breast Cancer in Asian Americans

Institution: University of Southern California
Study Start Date: June 1, 1995
Study End Date: May 31, 1999
Principal Investigator/Contact: Anna H. Wu, Ph.D.

Department of Preventive Medicine
University of Southern California
1441 Eastlake Avenue, MS #44
Los Angeles, CA 90033
323-865-0484
323-865-0139 (fax)

This population-based case-control study of breast cancer in Asian Americans is designed specifically to investigate the causes of their increase in breast cancer rates compared to their rates in Asia. The primary objectives are to test the following hypotheses: (1) a diet rich in soy products reduces the risk of breast cancer; (2) high intake of vegetables and fruits, particularly dietary fiber and specific micronutrients (e.g., beta-carotene, vitamin C), decreases the risk of breast cancer; (3) high intake of dietary fat increases the risk of breast cancer; (4) high physical activity reduces the risk of breast cancer; and (5) high body mass index and high waist-to-hip circumference ratio increase the risk of breast cancer. This study will include 350 Asian Americans (Chinese, Filipino, Japanese), ages 25 to 74, diagnosed with histologically confirmed, primary breast cancer identified in Los Angeles County. An equal number of Asian American women without breast cancer, matched to cases on age, ethnicity, and neighborhood, will be interviewed in person.

Gene-Diet/Tobacco Interactions in Breast Cancer in Asians

Institution: University of Southern California
Study Start Date: June 1, 1997
Study End Date: May 31, 2000
Principal Investigator/Contact: Anna H. Wu, Ph.D.

Department of Preventive Medicine
University of Southern California
1441 Eastlake Avenue, MS #44
Los Angeles, CA 90033
323-865-0484
323-865-0139 (fax)

Heterocyclic aromatic amines (HAs), polycyclic aromatic hydrocarbons (PAHs), and arylamines such as 4-aminobiphenyls (4-ABP) are mammary mutagens and carcinogens in rodents. Humans are exposed to those compounds primarily from diet (i.e., cooked meats), tobacco smoke, and certain occupations. If HAs, PAHs, and arylamines play a role in breast carcinogenesis in humans, then genetic polymorphisms in enzyme systems (N-acetyltransferases [NAT1 and NAT2], cytochrome P450 CYP1A1 [CYP1A1], and glutathione S-transferase M1 [GSTM1]) involved in the metabolism of these compounds are likely to influence the risk for breast cancer.

The main objective of this study is to use a PCR-based approach to investigate the roles of a series of metabolism genes (NAT1, NAT2, CYP1A1, and GSTM1) using materials and information collected from an ongoing case-control study of breast cancer in Asian Americans, which included 350 breast cancer cases and an equal number of controls. Additional breast cancer cases and population controls will be interviewed in the current study to ensure that there is sufficient study power to address the hypotheses of interest. The researchers expect that, at the completion of the parent case-control study and the current study, questionnaire data and DNA materials will be available on at least 500 breast cancer cases and a comparable number of population controls for genotypic comparisons.

3. CENTERS FOR DISEASE CONTROL AND PREVENTION/ NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Biomarkers of Occupational Disease Risk: Role in Human Carcinogenesis (Ecogenics of Breast Cancer)

Institution: Health Effects Laboratory Division, NIOSH
Study Start Date: 1997
Study End Date: N/A
Principal Investigator/Contact: Ainsley Weston, Ph.D. (Collaborators: Mary Wolff, Ph.D., Mount Sinai School of Medicine; Marilee Gammon, Ph.D., Columbia University; Regina Santella, Ph.D., Columbia University)

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Common DNA sequence variations (polymorphisms, a variant present in at least 1 percent of chromosomes, F=0.01) have come under scrutiny during the last decade. These investigations are association studies; they have evaluated certain polymorphic variants as breast cancer risk factors in epidemiologic studies. The studies that have considered individual polymorphisms have provided mixed results. No individual variant has been associated consistently with breast cancer risk. An alternative strategy in the identification of potential risk-bearing alleles is to condense multiple polymorphic loci into a haplotype. Whereas it can be argued that such a strategy expands the candidate base and leads to reduced power to detect a detrimental allele/variant, it can be countered that increased specificity is an absolute prerequisite when the overall lifetime risk associated with a relatively common variant is low.

This more recent approach has considered constellations of several polymorphisms that together form a haplotype. Several studies have now implicated a haplotype of three polymorphic loci in p53 (designated 1-2-1) as a breast cancer susceptibility factor. The lifetime risk associated with inheritance of $p53^{1\text{-}2\text{-}1}$ is relatively small, perhaps about 8 to 12 percent, but the frequency is high (10 to 15 percent); therefore, the public health consequences are important, since inheritance of this variant constitutes a factor in as many as 7,000 to 11,000 breast cancer cases annually. Moreover, the low lifetime risk estimate for inheritance of $p53^{1\text{-}2\text{-}1}$ is even more suggestive of a potential role for environmental or other genetic factors. A similar approach is being used to investigate BRCA1. The study group consists of Caucasians, African Americans, and Hispanics. For reasons that are unclear, the pathobiology of breast cancer in African Americans and

Hispanics differs from that in Caucasians, with mortality being the greatest in African Americans and onset being the earliest in Hispanics.

In its role as a "gatekeeper" and its role as the "grim reaper," it is even more pertinent to suggest the hypothesis that the breast cancer risk associated with inheritance of the $p53^{1\text{-}2\text{-}1}$ allele has an exposure component. The hypothesis is tested in this project using a complementary molecular epidemiologic approach where normal breast epithelial cells with known p53 genotype are exposed to specific in vitro chemicals. A second series of studies examines similar questions related to minor polymorphic variants of BRCA1 (these studies examine the role of polymorphisms and not frank mutations).

Effect of Exposure to Acetaminophen and Occupational/Environmental Chemicals on Breast Cancer

Institution: Health Effects Laboratory Division, NIOSH
Study Start Date: October 1996
Study End Date: October 1999
Principal Investigators/Contacts: Vincent Castranova, Ph.D., Linda J. Huffman, Michael Miller, Ph.D.

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The long-term goal of this research is to determine if concomitant exposure of women to some occupational/environmental chemicals and to acetaminophen increases breast cancer risk and/or alters the success of breast cancer therapy. Exposure to estrogen is one well-established breast cancer risk factor. Some chemicals, including specific pesticides, appear to exhibit estrogenic

activity, and it is thought that exposure to these chemicals may increase the overall body "estrogen" burden and increase risk of breast cancer. Studies in this laboratory demonstrated for the first time that therapeutic doses of acetaminophen also act like estrogen, in that acetaminophen stimulates the growth of estrogen-responsive breast cancer cells maintained in the laboratory (in culture). Because acetaminophen (Tylenol) is used in more than 850 drug formulations and commonly is used by millions of women, men, and children, it may be one factor that contributes to breast cancer risk in some individuals. Women in agricultural areas and female migrant workers do not have easy access to physicians and hospitals and tend to self-medicate with drugs (over-the-counter and prescription), many of which contain acetaminophen. These women also are exposed to pesticides more than the general population. Thus these women represent underserved populations that may be receiving high doses of chemicals that may alter breast cancer risk.

4. DEPARTMENT OF DEFENSE

Novel Recruitment Techniques for a Study of Culture-Specific Diet, Metabolic Variability, and Breast Cancer Risk in African American Women

DoD Division: USAMRMC
Institution: Food and Drug Administration/National Center for Toxicological Research
Study Start Date: June 1998
Study End Date: May 2001
Principal Investigator/Contact: Christine B. Ambrosone, Ph.D.

Division of Molecular Epidemiology
National Center for Toxicological Research
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Jefferson, AR 72079
870-543-7528
870-543-7773 (fax)

Among African American women younger than age 50, breast cancer incidence is almost twice that of Caucasian women. African American women are more often diagnosed with aggressive tumors and have higher mortality rates than Caucasians. Differences in tumor biology and mortality do not appear to be due to factors related to socioeconomic status. Little is known regarding explanations for these racial disparities, perhaps because of the difficulty in enrolling African Americans in research studies. In general, poor participation of potential cases and controls is becoming a growing problem in all research studies but is of particular concern for studies of minority health.

The researchers propose a novel method of recruitment in this pilot study to investigate previously unexplored risk factors that could account for the more virulent nature and early onset of breast cancer in African American women. Through rapid case ascertainment by the Tumor

Registries in Arkansas, approximately 260 cases will be enrolled over 2 years and frequency-matched to controls randomly selected from Health Care Finance Administration lists and State Identity Card lists. Cases and controls will be contacted first by a letter from their hospital in support of the study, then by an introductory postcard from a breast cancer survivor from their town or county with her photograph on it. This will be followed by a call from that recruiter. These breast cancer survivors have been trained in community outreach and breast cancer education through the Witness Program™. Participants will be interviewed by culturally appropriate women, and blood and urine specimens will be obtained to explore study hypotheses. Racial differences in cancer incidence could be related to genetic or environmental factors. The researchers propose that some of the racial variability in incidence and aggressiveness of breast cancer could be attributed to an interaction of the two.

Dietary practices of African American women, particularly in the rural south, differ markedly from those of Caucasian women, and traditional Food Frequency Questionnaires (FFQ) do not accommodate these food habits. Thus, these FFQs may not account for major contributors of fat and food-derived heterocyclic amines, known mammary mutagens and carcinogens, to the diet. The Block Health Habits Questionnaire will be adapted for this population, based on results of a survey the researchers currently are conducting to assess frequency of consumption of 60 foods commonly eaten by African Americans in Arkansas, elicited by African American focus groups. Heterocyclic amines will be assessed using a questionnaire developed for this purpose. The researchers intend to evaluate the role that diet particular to African Americans in the rural South may play in breast cancer etiology and to assess the possible modification of risk by genetic differences in metabolism.

Specifically, the researchers will evaluate the interaction of dietary sources of heterocyclic amines with polymorphisms in N-acetyltransferases (NAT1 and NAT2), cytochrome P4501A2, and sulfotransferase, all of which are involved in their metabolism. Genetic polymorphisms in CYP1A2 and sulfotransferase have not yet been evaluated in population studies, nor has the interaction of any of these polymorphisms been applied to risk associated with heterocyclic amines, especially in African American women. There is wide variability in ethnic distribution of polymorphisms, and higher prevalence of those related to rapid activation of heterocyclic amines, with greater consumption of sources of heterocyclic amines, may put African American women at greater risk for more aggressive breast cancer at an earlier age. The methodology for control selection, interviewer training and monitoring, questionnaire development, and data entry and analysis have been developed in the context of an ongoing molecular epidemiologic case-control study of colorectal cancer by some of these investigators. Development of strategies to encourage minority participation in research studies will be of great importance for success in future epidemiologic studies of breast cancer. Additionally, the collection of pilot data to evaluate innovative hypotheses regarding potential breast cancer risk factors particularly relevant to African American women may lay the groundwork for a larger study including African American and Caucasian women to further elucidate factors in the etiology of breast cancer and identify susceptible subgroups of women.

Diet, Genetic Polymorphisms, and Breast Cancer in African Americans

Institution: Howard University Cancer Center
Study Start Date: September 16, 1998
Study End Date: September 15, 2001
Principal Investigator/Contact: Lucile L. Adams-Campbell, Ph.D.

Howard University Cancer Center
2041 Georgia Avenue, NW, Room 220
Washington, DC 20060
202-806-7697
202-667-1686 (fax)

The goal of this project is to identify nonhormonal dietary risk factors and genetic susceptibility for breast cancer in African American women.

The Relationship Between Endocrine Factors and Breast Cancer Risk

Institution: Howard University Cancer Center
Study Start Date: August 15, 1997
Study End Date: September 1999
Principal Investigator/Contact: Tanya Agurs-Collins, Ph.D.

Howard University Cancer Center
2041 Georgia Avenue, NW
Washington, DC 20060
202-865-4674
202-667-1686 (fax)

Dr. Agurs-Collins is studying the relationship between endocrine factors and risk of breast cancer. Specifically, she is conducting an epidemiologic study on IGF-1 (insulin-like growth factor—type 1) and breast cancer risk among postmenopausal African American women. Dr. Agurs-Collins also is including in the study other risk factors, such as physical activity, central adiposity, and hyperinsulinemia. The research design is a case-control study of women who are 55 to 79 years of age.

BRCA1 and BRCA2 Mutations in African Americans

DoD Division: Department of the Army
Institution: Howard University Cancer Center and Department of Biochemistry and Molecular Biology, Howard University College of Medicine
Study Start Date: September 1998
Study End Date: September 2001
Principal Investigator/Contact: Carolyn Broome, Ph.D.

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202-806-5039
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Mutations in the breast cancer predisposing genes BRCA1 and BRCA2 have not been extensively and systematically investigated in African Americans. BRCA1 and BRCA2 mutations will be investigated in 55 or more high-risk African American breast cancer patients with a family history of breast/ovarian cancer or early-onset breast cancer. The entire coding region for BRCA1 and BRCA2 will be analyzed by single-stranded conformational polymorphism, the protein truncation test, and the DNA chip assay. All putative mutations/variations will be confirmed by DNA sequencing. Mutations/variations detected in patients will be tested in other affected and unaffected family members and in 100 control individuals from the general African American population, not selected for disease. Intron mutations will be investigated by the protein truncation test using mRNA. Missense mutations that are not observed in controls will be tested in functional assays for BRCA1 and BRCA2 to determine cancer association.

By studying a large number of high-risk African American breast cancer patients, the BRCA1 and BRCA2 mutations that are most common in the African American population will be detected. Since BRCA1 and BRCA2 mutations are known to vary with the population studied, mutations in African Americans are expected to differ from those reported in other populations. Breast cancer predisposing mutations detected in African Americans will be examined in 200 additional African American breast cancer patients and in the 400 controls from the general African American population using allele-specific multiplex polymerase chain reaction. This preliminary study will provide information about the BRCA1 and BRCA2 frequency in African American breast cancer patients and will provide information for a more statistically significant general population study, risk assessment, genetic counseling, and treatment in African Americans.

ER in Breast Cancer

Institution: Howard University College of Medicine
Study Start Date: October 1, 1994
Study End Date: 1998
Principal Investigator/Contact: Indra Poola, Ph.D.

Departments of Pharmacology and Biochemistry and Molecular Biology
Howard University College of Medicine
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Washington, DC 20059
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Dr. Poola is developing new molecular biological approaches to evaluate prognostic factors in breast tumors. Molecular methods have been developed for the quantification of mRNA copy number of the most important prognostic factor, the estrogen receptor, based on RT PCR template competition approach. As a standard of reference, methodologies for the quantification of mRNA copy numbers of the housekeeping gene, the glyceraldehyde-3-phosphate dehydrogenase, also have been developed. A novel primer design has been developed for the specific detection of ER mRNA splice variants in breast tumors. New molecular approaches for the quantification of ER mRNA splice variant copy numbers in breast tumors also have been developed. Dr. Poola is using samples from whites and African Americans and will examine differences between these groups.

Methyl-Deficient Diets and Risk of Breast Cancer Among African American Women: A Case-Control Study by Methylation Status of the ER Genes

Institution: Meharry Medical College
Study Start Date: October 1997
Study End Date: September 2000
Principal Investigator/Contact: Kangmin Zhu, M.D., Ph.D.

Department of Occupational and Preventive Medicine
Meharry Medical College
1005 D.B. Todd Boulevard
Nashville, TN 37208
615-327-6150
615-327-5834 (fax)

Previous epidemiological studies using ER levels as a measurement of ER status have obtained inconsistent results on whether ER-negative and ER-positive breast cancers have different risk factor profiles. Recent molecular studies show that ER-negative breast cancer results from the lack of ER gene transcription due to the methylation of the CpG island 5' to the gene. Because methyl-deficient diets can lead to abnormal DNA methylation and, therefore, carcinogenesis, the researchers hypothesize that these diets are more likely to be associated with tumors with methylated ER genes. Interactions between the diets and other risk factors such as hormone-related risk factors also may differ according to the methylation status of the ER genes. The overall goal of this study is to examine the relationship between methyl-deficient diet and breast cancer according to the methylation status of the ER genes among African American women.

This study will use a case-control design. Female African American patients ages 64 or younger who are diagnosed with breast cancer during 1995 to 1997 will be eligible as cases if they live in Davidson, Shelby, or Hamilton Counties, Tennessee, and have household telephone services. The cases will be identified and selected through the Tennessee Cancer Reporting System. Controls will comprise African American women without breast cancer who will be selected through random-digit telephone dialing and frequency matched to cases according to age and residence area. Information on dietary methyl components and other risk factors will be collected from telephone interviews. Information on ER status and tumor diagnosis will be

obtained from medical records and Tennessee Cancer Reporting System files. Tissue specimens will be collected for the measurements of ER levels and the methylation status of the ER genes. Polytomous logistic regression method will be used to examine if the relationship between methyl-deficient diets and breast cancer risk differs by methylation status of the ER genes. The information from the telephone interviews and medical records for 1995 to 1996 cases and controls will come from a study that has been recommended to receive funding from the Department of Defense.

Using the information collected, the researchers will be able to specifically examine (1) whether the methyl-deficient diet/breast cancer relationship differs depending upon the methylation status of the ER genes in African American women and (2) whether interactions between methyl-deficient diets and other risk factors differ according to the methylation status of the ER genes of tumors.

Racial/Ethnic Differences in Breast Cancer Risk Factors

Institution: Northern California Cancer Center
Study Start Date: July 1, 1996
Study End Date: June 30, 2000
Principal Investigator/Contact: Esther M. John, Ph.D.

Northern California Cancer Center
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Suite 600
32960 Alvarado-Niles Road
Union City, CA 94587
510-429-2554
510-429-2550 (fax)

Despite striking differences in incidence rates, breast cancer is the leading incident cancer in women of all racial/ethnic groups. Yet most analytic epidemiologic studies have been conducted in white women. Little is known about breast cancer risk factors in African American and Hispanic women. The researchers are conducting a population-based case-control study in the San Francisco Bay area among African American and white women using the same methodology and questionnaire as an ongoing case-control study of breast cancer in Hispanic women. Combining the data for the three racial/ethnic groups, they will examine the risk factor profile (e.g., prevalence of risk factors, magnitude of associations with risk factors) among white (high-risk), African American (intermediate-risk), and Hispanic (low-risk) women in order to elucidate the reasons for the pronounced racial/ethnic differences in breast cancer incidence rates.

Cases include all African American women and a 10 percent sample of white women ages 35 to 79 years who were diagnosed with breast cancer between 1995 and 1998 and resided in the San Francisco Bay area at the time of diagnosis. Cases are ascertained through the population-based cancer registry of the Greater Bay area. African American and white controls living in the San

Francisco Bay area are identified through random-digit dialing and are frequency-matched to cases by 5-year age group in a ratio of one control per case.

Professional interviewers conduct home visits and administer a structured questionnaire and measure skin pigmentation and anthropometry (i.e., weight, height, hip and waist circumferences). The interview collects information on demographic background, residential history, physical activity, sunlight exposure, diet, supplement use, body size, change in weight, occupational history, pregnancy and menstrual history, hormone use, and medical history. The researchers estimate that they will complete interviews and measurements for 330 African American and 365 white cases and equal numbers of controls by the summer of 1999.

Combining the interview data and measurements for the three racial/ethnic groups, the researchers will examine breast cancer risk factors separately for African Americans (380 cases and controls) and whites (460 cases and controls) and compare their risk factor profile with that of Hispanics (510 cases and 760 controls). Specifically, the researchers will compare the prevalence of risk factors among controls and the magnitude of relative risks associated with the risk factors. Performing attributable risk calculations, they will estimate to what extent differences in the magnitude of relative risks and/or prevalence of risk factors account for the pronounced differences in breast cancer incidence rates in these populations. The data analysis will be completed by May 2000.

Ethnicity, Soy Bean Consumption, and Mammographic Density Patterns

Institution: University of Hawaii
Study Start Date: September 1, 1996
Study End Date: August 31, 1999
Principal Investigator/Contact: Gertraud Maskarinec, M.D., Ph.D.

University of Hawaii
Cancer Research Center of Hawaii
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808-586-3078
808-586-3009 (fax)

Breast cancer risk in the United States is higher for Caucasian and Native Hawaiian than for Asian women. Dense patterns in healthy mammograms have been shown to be related to a higher breast cancer risk. Therefore, the researchers propose that mammograms from Caucasian and Hawaiian women have denser patterns than mammograms from Asian women. Soy foods may be one of the dietary factors that protect Asian women against breast cancer. This study compares mammograms from women with different ethnicities and diet.

Healthy women of Japanese, Chinese, Filipino, Caucasian, and Native Hawaiian ancestry are being recruited at several mammography clinics in Hawaii. Women with normal mammograms provide information on their medical history, dietary habits, weight, and height. With the help of

a computer, the total area of the breast on the mammogram and the areas appearing dense are measured. The researchers are investigating the relation between ethnicity, diet (in particular, soy foods), and the appearance of the healthy mammograms. The importance of this research is the potential to identify dietary factors in women from ethnic groups with a low risk for breast cancer that may lead to prevention studies in women at high risk for breast cancer.

5. NATIONAL INSTITUTES OF HEALTH/NATIONAL CANCER INSTITUTE

Case-Control Study of DMPA and Breast Cancer

Institution: Boston University
Study Start Date: 1993
Study End Date: 1998
Principal Investigator/Contact: Samuel Shapiro, M.B. (Co-Investigator: Lynn Rosenberg, Sc.D.)

Slone Epidemiology Unit
Boston University School of Public Health
1371 Beacon Street
Brookline, MA 02446
617-734-6006
617-738-5119 (fax)

Boston University, in conjunction with the University of Cape Town, has conducted a case-control study on the role of contraceptive methods in breast cancer risk among South African women of African and mixed ancestry to assess the risk of breast cancer in relation to use of depot medroxyprogesterone acetate (DMPA) and oral contraceptives. Reproductive factors also will be studied.

Followup Study for Causes of Illness in Black Women

Institution: Boston University
Study Start Date: 1994
Study End Date: N/A
Principal Investigator/Contact: Lynn Rosenberg, Sc.D. (Co-Investigators: Julie R. Palmer, Sc.D., Lucile L. Adams-Campbell, Ph.D.)

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This effort is a large prospective followup study of African American women aimed at providing informative data on risk factors for cancer, cardiovascular disease, and other major illnesses. In 1995, researchers enrolled—by means of a mailed questionnaire—64,554 African American women 21 to 69 years of age from all parts of the United States. The 1995 questionnaire collected information on exposures and covariates of interest. Followup mail questionnaires at 2-year intervals will update information and ascertain incident cases of cancer, cardiovascular disease, and other major illnesses. The first such followup questionnaire was sent in 1997. Diagnoses are documented by review of medical records and other documents. Deaths are ascertained from families and friends and through the National Death Index. This study will provide needed information on the etiology of disease in African American women, a heretofore neglected group in health studies.

Case-Control Surveillance Study of Medications and Cancer

Institution: Boston University
Study Start Date: 1976
Study End Date: 2002
Principal Investigator/Contact: Lynn Rosenberg, Sc.D. (Co-Investigators: Julie R. Palmer, Sc.D., Samuel Shapiro, M.B., Brian Strom, M.D.)

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Since 1976, patients in participating hospitals have been interviewed about lifetime history of medication use and other factors (e.g., cigarette smoking, medical history) that may influence the risk of cancer. Over 75,000 patients, including 25,000 with newly diagnosed cancers of various sites, have been interviewed. Twenty percent of the participants are members of minority populations. The database has served as a resource for conducting case-control analyses to assess the relationship of medications to the occurrence of cancer. Other factors have been assessed as well. Over 60 publications have been based on these data. Adverse effects, protective effects, and safety have been documented. Results will be compared across racial and ethnic groups if appropriate.

Benign Breast Disease: Molecular Differentiation of Risk

Institution: Case Western Reserve University and Henry Ford Hospital
Study Start Date: October 1, 1996
Study End Date: September 30, 2001
Principal Investigator/Contact: Maria J. Worsham, Ph.D.

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Although the risk of breast cancer for women in the United States is approximately one in nine, identification of risk factors and translation of that knowledge into strategies for prevention have been inhibited by poor understanding of disease pathogenesis. A few benign breast proliferations are associated with higher risk of breast cancer, but definition of a preneoplastic morphologic continuum is lacking. The investigators are studying 5,353 eligible women, derived from a large multiethnic population, who were diagnosed by biopsy with benign breast disease (BBD) between 1981 and 1991. They were followed from 5 to 15 years, yielding an estimated 248 women who will have developed invasive breast cancer. This case-control study is using tissue samples, pathology reports, and epidemiologic data to (1) ascertain the incidence and time span of breast cancer development in this cohort, (2) to estimate the frequency of selected genetic alterations in both BBD and invasive cancers from the same individuals in a subset of the cohort, and (3) using a nested case-control approach, to evaluate risk factors for breast cancer among women with BBD, including specific histological characteristics, molecular markers, family history of breast cancer, and reproductive history.

The purpose of the study is to evaluate the importance of biomarkers for risk for breast cancer development and to determine their contribution to the definition of a genetic sequence in breast carcinogenesis.

Assessment of genetic alterations will employ fluorescent in situ hybridization and PCR. Investigators will identify chromosomal aneuploidy, selective with respect to individual chromosomes and as a measure of DNA ploidy, and HER-2/neu amplification patterns in BBD and invasive cancer. They will identify p53 mutations by single-strand conformation analysis (SSCP), determine clonality using the PCR nested primer approach for the PGK locus (on Xq arm), and assess loss of heterozygosity (LOH) for intragenic markers of the BRCA1 (17q21) and E-cadherin (16q22) genes. When LOH is observed, analysis of the genes using SSCP will attempt to identify the putative mutations. Lack of a constitutional BRCA1 mutation will rule out one form of inherited breast cancer, allowing subtyping of the remaining tumors by histopathological and genetic profiles and time frame of cancer development. This study should help establish a genetic and morphologic continuum from BBD to breast cancer and provide a firmer basis for interpretation of the roles of known risk factors, with the eventual objective of permitting targeted testing of preventive strategies and therapeutic regimens. The data will be examined across races.

Plasma Insulin-Like Growth Factor-I (IGF-I) and IGF-Binding Protein 3 (IGFBP3) in Minority Breast Cancer Patients: Correlation With Clinical Parameters*

Institution: Charles R. Drew University of Medicine and Science
Study Start Date: N/A
Study End Date: N/A
Principal Investigator/Contact: Jaydutt Vadgama, Ph.D.

Department of Internal Medicine
Molecular Oncology Program
Charles R. Drew University of Medicine and Science
1621 East 120th Street
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In vitro studies have demonstrated that IGF is a mitogen for breast cancer cells. However, the association of plasma IGF-I with tumor histopathology in high-risk groups needs further investigation. The researchers hypothesized that plasma IGF-I and serum IGFBP3 concentrations in breast cancer patients may provide useful information on the progression of their disease and determine the probability of recurrence and survival.

The researchers have carried out a retrospective study on 130 minority breast cancer patients. Plasma IGF-I and serum IGFBP3 were correlated with tumor histopathology, menopausal stages, treatment modality, recurrence rates, and probability of survival. Plasma IGF-I and serum IGFBP3 were measured by radioimmunoassay.

The studies confirm that breast cancer patients have elevated plasma IGF-I and serum IGFBP3 levels. In addition, the researchers observed the following: IGF-I did not correlate with age and nodal stage. IGF-I and IGFBP3 increased with tumor size (T4). IGF-I did not correlate with estrogen receptor status, but it did increase in PR-positive patients. IGF-I levels were higher in premenopausal patients and in women with cancer recurrence. Tamoxifen reduced IGF-I levels significantly and reduced the risk of recurrence. The survival probability was greater in patients with plasma IGF-I levels less than 120 ng/ml.

Researchers concluded that the lowering of plasma IGF-I offers the following benefits: (1) reduction in the risk of developing breast cancer in high-risk groups, (2) slowing of the progression of breast cancer in patients with early stages of cancer, (3) lowering of the risk of recurrence, and (4) increase in the probability of survival.

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* Also funded by NIH/NCRR.

Racial Differences in Breast Cancer Survival

Institution: Emory University
Study Start Date: 1994
Study End Date: June 2001
Principal Investigator/Contact: Elaine W. Flagg, Ph.D.

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This case-control study is examining reasons for the threefold survival difference observed between African American and white women by examining women ages 20 to 54 in Atlanta who are newly diagnosed with invasive breast cancer. The study focuses on three issues: (1) the extent of racial differences in the aggressiveness of breast cancers and the contribution of method of detection to racial differences in tumor aggressiveness, (2) the effects of adolescent exposure to several hormone-related breast cancer risk factors and of the method of breast cancer detection on tumor aggressiveness and on racial differences in tumor aggressiveness, and (3) the contribution of tumor aggressiveness to poorer survival rates among African American women. This project builds on information already collected on 841 women with invasive breast cancer (246 African American, 595 white) and 914 controls (251 African American, 633 white) who were interviewed as part of an NCI-initiated, population-based case-control study of breast cancer etiology in young women (N01-CP-95642-32). All women newly diagnosed with invasive breast cancer in Fulton, DeKalb, and Cobb Counties in Georgia during May 1, 1990, to December 31, 1992, were identified, and 87 percent of African American women with breast cancer and 90 percent of white women with breast cancer were interviewed. A sample of controls was selected from the same counties during the same time period, and 83 percent were interviewed. This patient cohort will be followed for recurrence and mortality through April 2000. Patient interview information is already available on screening history, method of cancer detection, and primary risk factors of interest: early menarche and adolescent exposure to oral contraceptives, spontaneous and induced abortion, childbirth, and obesity. A detailed pathologic review will be conducted and two markers of cell proliferation will be measured in formalin-fixed, paraffin-embedded tissues: S-phase fraction determined by flow cytometry and Ki-67 by immunocytochemical staining. Four other well-characterized markers of tumor aggressiveness are a focus of this analysis: aneuploidy (DNA content measured by flow cytometry), expression of c-erbB-2 and p53 gene products (detected by immunocytochemistry), and vascular response (determined by image quantification of vascular density). The study includes information on a variety of additional characteristics that affect risk and/or survival.

A supplemental component of this study being conducted by a doctoral student working with Dr. Flagg aims to determine if the anthropometric differences (e.g., differences in weight, height, bra

cup size, wrist circumference, elbow to wrist length) between African American and white women account for different survival rates.

Inherited Breast Cancer in Chinese Women

Institution: Fred Hutchinson Cancer Research Center
Study Start Date: September 30, 1997
Study End Date: September 29, 2000
Principal Investigator/Contact: Elaine A. Ostrander

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Fred Hutchinson Cancer Research Center
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The goal of this study is to describe the frequency and type of mutations and polymorphisms in two autosomal dominant, highly penetrant breast cancer genes in cases and controls from a population-based series of Chinese women with breast cancer, unselected for family history. Mutations in the BRCA1 and BRCA2 genes all have been associated with breast cancer in high-risk families that include multiple cases of apparently inherited disease, often at a young age. The majority of these data derive from studies of a small number of high-risk white families with unusually high frequencies of early-onset breast cancer. Little information is available regarding the frequency, type, or presence of founder mutations in other populations, specifically among Asians. As a result, no information is currently available for genetic testing or screening for either Chinese women or Western women living in North America or Europe who are of Chinese descent. This study seeks to provide and disseminate that information by (1) determining the frequency and types of mutations in the BRCA1 genes in cases and controls from a large, population-based study of breast cancer in Shanghai, China; (2) developing a public database to distribute the above information, along with information regarding the type and frequency of polymorphisms and rare sequence variants; and (3) comparing the frequency and type of mutations with suspected risk factors for breast cancer. This study will be nested within the Shanghai Breast Self-Examination Trial, a randomized controlled trial of 267,000 women designed to examine the effect of breast self-examination on breast cancer mortality in Shanghai. The extensive epidemiologic data that are already available on this cohort may be combined with data collected in this study for additional analyses. Information from the above studies could be used to formulate public health policy and diagnostic breast cancer screening strategies on subsets of Asian women in the future.

Gene Regulation in Breast, Colon, and Skin Cancer*

Institution: Howard University Cancer Center
Study Start Date: September 1994
Study End Date: September 1998 (renewal application submitted)
Principal Investigator/Contact: Agnes Day, Ph.D.

Howard University Cancer Center
2041 Georgia Avenue, NW, Room 406
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202-806-7578
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Dr. Day, in collaboration with Dr. Matthew George, Jr. (Howard University), is conducting an investigation into the role of gene regulation in cancer with the aim of developing clinical profiles for breast, colon, and skin cancer metastasis. In the breast cancer portion of the study, she will look at a battery of breast tissue types in African American, Hispanic, and white women from the Washington, DC, area and will collect information on race, age, and tumor type. The types of tissues studied will include tissue from cell lines, normal tissue, fibrocystic (anomalous) tissue, primary breast cancer tissue, and secondary metastatic breast cancer tissue.

Dr. Day notes that when a primary tumor metastasizes, the cancer cells break out of the tumor and enter the bloodstream, travel to a new site or stop in the bone, and form a secondary tumor. In order to do so, the cells must pass through the connective tissue and basement membranes surrounding the organs where the primary and the secondary tumors are located. She hypothesizes that tumor cells may produce high levels of metalloproteases (enzymes that digest connective tissue) and, at the same time, signal the genes responsible for producing the proteins that make up connective tissue and basement membranes to turn off production. These biochemical activities would reduce the amount of connective tissue around target organs, allowing tumor cells to pass more easily from one to another.

Using RNA and DNA from biopsies of breast tissue, Dr. Day will probe with cDNA clones (short fragments of "complementary" DNA used to measure the level of activity in target regions of complete RNA or DNA strands) to determine the levels of connective tissue proteins in the various types of breast tissue collected. The specific proteins under investigation are decorin, osteonectin, type I collagen, type II collagen, and fibronectin. These proteins are involved in the formation of the connective tissue matrix and basement membrane that surround and separate each organ of the human body. If Dr. Day's hypothesis is correct, levels of these proteins should be lower in cancerous tissue than normal tissue and lower in metastatic tumor tissue than in primary tumor tissue. Results of these studies may allow clinicians to determine if a primary tumor has metastasized and, thus, reduce or increase chemotherapy/radiotherapy.

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* Also funded by the NIH/MBRS Program.

Risk Factors for Breast Cancer Among Women in China

Institution: Kaiser Permanente
Study Start Date: July 1998
Study End Date: Summer 2002
Principal Investigator/Contact: De-Kun Li, M.D., Ph.D.

Division of Research
Kaiser Permanente
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510-450-2255

This study is a 4-year retrospective case-control study to examine breast cancer risk factors among women in China. Dr. Li wants to compare the magnitude of relative risk for breast cancer among women in developing countries (China) to those in developed countries (United States). Data will be collected on reproductive factors, including induced and spontaneous abortion and age at first birth. Impact of the change in diet also will be studied (the Chinese diet increasingly has included more animal fat and, therefore, has become more like the American diet). Once analyzed, results from this study will be compared with those from past U.S. studies. This study also will examine the effects of occupational exposures.

Breast Cancer and Risk Factors Among African American Women Aged 20 to 64: A Case-Control Study According to Estrogen Receptor Status

Institution: Meharry Medical College
Study Start Date: September 1996
Study End Date: February 1999
Principal Investigator/Contact: Kangmin Zhu, M.D., Ph.D.

Department of Occupational and Preventive Medicine
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The overall goal of this project is to examine what factors may increase the risk of breast cancer and to evaluate whether risk factor profiles differ according to ER status of the disease among African American women. The study will increase the limited knowledge of risk factors for breast cancer among African American women.

This study will use a case-control design. Cases will consist of 220 African American women ages 20 to 64 who were diagnosed with breast cancer during 1992 to 1993 and who lived in Davidson and Shelby Counties, Tennessee. The cases will be identified and selected through the

Tennessee Cancer Reporting System. Controls will be African American women without breast cancer who will be selected through random-digit telephone dialing and frequency-matched to cases according to age range and residence area (n=440). Information on risk factors and tumor diagnosis will be collected from telephone interviews, medical records, and Tennessee Cancer Reporting System files. Polytomous logistic regression method will be used to examine if risk factor profiles differ between ER-positive and ER-negative tumors. Segregation analysis will be adopted to explore major gene effects of the disease among families of the cases.

Using the information collected, the researchers will be able to specifically examine (1) if risk factors for breast cancer differ depending upon ER status of the disease among African American women, (2) whether there are any interactions between different risk factors according to ER status of cancer, and (3) whether familial patterns and major gene effects vary with ER status of the disease.

Breast Cancer in Women of Polish Ancestry

Institution: Michigan State University
Study Start Date: October 1, 1997
Study End Date: July 30, 2002
Principal Investigator/Contact: Dorothy Rybaczyk Pathak, Ph.D.

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College of Human Medicine
Michigan State University
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Breast cancer incidence among Polish women is one-third that of U.S. women (age-adjusted rates per 100,000 in 1990: Warsaw City, 37; Warsaw Rural, 18; and in 1985 to 1989: U.S. whites, 94). Yet, recent studies of Polish immigrants to the West showed breast cancer mortality rates for immigrants similar to the rates of the host country (standardized mortality ratios: 91 [United States], 100 [Australia], and 97 [England and Wales]). No other population of migrants has shown so rapid a transition. The short time needed to express this changing risk for breast cancer implicates modifiable environmental factors as significant determinants of risk. To evaluate the role of these factors, characteristics of place of origin and destination, change in habits, and when these changes occurred, as well as the individual's characteristics that influence breast cancer risk, must be assessed.

The researchers are conducting two parallel, population-based case-control studies of breast cancer cases in 20- to 74-year-olds in two populations: (1) Polish-born immigrants (378 cases and 378 controls) residing in Cook County and Detroit metropolitan area, and (2) Polish-native individuals (500 cases and 500 controls) residing in Warsaw City.

The researchers hypothesize that components of both usual adult and past diet are associated with breast cancer risk. They hypothesize that, after adjusting for established risk factors, breast cancer risk will be increased by (1) reduction in intake of specific types of foods such as cruciferous vegetables, root vegetables, whole grain breads, and other cereals, and thus (2) reduction in intake of phytochemicals (e.g., glucobrassicins, carotenoids, flavonoids, antioxidants) and dietary fiber; (3) increase in intake of meat, meat products, and dietary fat; and (4) interaction among the dietary constituents in 1 through 3 above. Assessment of dietary intake at two points in life (late 1980s representing usual adult diet and premenarcheal) will provide insight into whether there are key ages at which dietary factors alter breast cancer risk.

This study brings together disparate areas of breast cancer research (nutrition, epidemiology, changes in risks due to migration) in strategically selected populations with a threefold difference in breast cancer mortality to develop a critical understanding of the nutritional risk factors and their implications in breast cancer etiology. The proposed study will examine the role of emerging and established risk factors for breast cancer and their interactions. Thus, results from this study should help clarify the ambiguous findings for dietary fat and will contribute to understanding the role specific vegetables and phytochemicals play in lowering breast cancer risk, with clear implications for breast cancer prevention.

Genetic Mutations in Malignancy

Institution: Morehouse School of Medicine
Study Start Date: August 15, 1995
Study End Date: June 30, 1999
Principal Investigator/Contact: Deborah Ann Lyn, Ph.D.

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Tumor progression has been viewed as a genetic process in which a developing cancer cell acquires somatic mutations in growth regulatory gene(s). Each successive molecular change grants the cell a growth or survival advantage. In addition, the deregulation of prominent cell cycle-related proteins contributes to tumor formation. The purpose of this study is to address whether the high incidence and mortality of breast and gynecological cancers in African American women are associated with an increased frequency of mutations in cancer susceptibility genes. Tumor samples have been analyzed for mutations in p53 and the recently identified tumor susceptibility gene, PTEN/MMACI. Similar mutational frequencies were observed in these genes compared to studies conducted in other population groups. Other tumor biologic factors such as p16 expression and protein accumulation of G1 cyclins were examined simultaneously in the same group of samples. Loss of p16 expression was the most frequently

observed abnormality present in this cohort of breast tumors. It is expected that this approach will lead to the development of a comprehensive database to enumerate which combinations of molecular changes are associated with particular tumor types.

Prevalence of BRCA1: A Population-Based Study

Institution: Mount Sinai School of Medicine
Study Start Date: July 1, 1996
Study End Date: August 31, 1999
Principal Investigator/Contact: Jonine L. Bernstein, Ph.D.

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The recent discovery and cloning of the BRCA1 gene (Miki 1994), which predisposes to breast and ovarian cancers, corroborates extensive genetic and epidemiologic data on familial patterns of inheritance and establishes a genetic contribution to their etiology. To estimate the distribution and characteristics of BRCA1 mutations in a population-based series of breast and ovarian cancer cases, the researchers propose to retrieve 1,355 paraffin-embedded breast tissue blocks from young African American and white women diagnosed with breast cancer between 1980 and 1982 who were part of a large, multicenter, population-based case-control study. Tissue blocks from 250 women with ovarian cancer, who were part of the same parent study, already have been collected. For all cases, extensive risk factor and followup information also have been collected and computerized.

The goals of this study are (1) to explore the frequency, location, and type of germline BRCA1 mutations among a population-based sample of young African American and white women with breast and/or ovarian cancer, with and without a family history of cancer; (2) to describe the clinical features of genetic subtypes of breast and ovarian cancers diagnosed in African American and white women who have specific germline mutations (or groups of mutations) of the BRCA1 gene; (3) to determine risk factors for genetic subtypes of breast and/or ovarian cancer (as defined by mutations, or groups of mutations, of the BRCA1 gene) among African American and white women; and (4) to evaluate the possibility of somatic mutations in a population-based study of women with breast or ovarian cancer. BRCA1 analyses of the paraffin-embedded tissue specimens will be performed using a three-stage approach for efficient mutation detection: (1) allele-specific nucleotide (ASOs), (2) RNase mismatch, and (3) PCR-based sequencing. This approach already has been operationalized in the researchers' laboratories.

This study will provide comprehensive information in an epidemiologic context on the contribution of BRCA1 to the etiology of breast and ovarian cancers, and it will guide the

development of accurate counseling of and effective intervention strategies for women who carry high-risk alleles.

Molecular Epidemiology of Breast Cancer

Institution: Mount Sinai School of Medicine
Study Start Date: April 1, 1997
Study End Date: April 30, 2000
Principal Investigator/Contact: Jonine L. Bernstein, Ph.D.

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Breast cancer is a heterogenous disease with multiple etiologic and molecular pathways. To help elucidate the basis for this heterogeneity, the researchers propose (1) to describe the prevalence of overexpression of HER-2/neu and p53 in a large population-based study of breast cancer patients, (2) to relate known or hypothesized risk factors for breast cancer to the prevalence of overexpression of HER-2/neu and p53, (3) to assess whether overexpression of HER-2/neu or p53 is associated with differential survival, (4) to estimate the degree of association between race and the incidence of breast cancer with overexpression of HER-2/neu or p53, and (5) to distinguish particular patterns of molecular alterations that predict the incidence of second primary breast cancer.

Specifically, the researchers will retrieve 1,544 paraffin-embedded breast tumor tissue blocks for women diagnosed with breast cancer between 1980 and 1982 who were part of a large population-based case-control study. Extensive risk factor and followup information already have been collected and computerized. Paraffin blocks will be analyzed for overexpression of the p53 tumor suppressor gene and the HER-2/neu oncogene using immunohistochemical staining techniques. The researchers' hypothesis is that the identification of pathologically unique subtypes of tumors will bear a stronger relationship with certain risk factors. The purpose of this study is to correlate epidemiologic risk factor information with specific molecular changes to differentiate these etiologic subgroups and to respond to the aims as briefly stated above.

Environmental and Genetic Determinants of Breast Cancer*

Institution: Mount Sinai School of Medicine
Study Start Date: N/A
Study End Date: September 1998
Principal Investigator/Contact: Mary S. Wolff

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The researchers are completing a case-control study of breast cancer risk among women, including minorities, in the New York metropolitan area with respect to environmental factors, carcinogen metabolizing enzymes, and oncogens.

Levels of organochlorines (1,1-dichloro-2,2`-bis(p-chlorophenyl)-ethylene [DDE] and poly-chlorinated biphenyl [PCB]) in blood serum are being compared between breast cancer cases and two control groups. Early results indicate higher levels of DDE among African American and Hispanic women and higher levels of PCBs among African Americans. Genetic polymorphisms in carcinogen-metabolizing genes (i.e., CYP1A1, CYP17, CYP2E1, GST) have been determined. Interactions of environmental exposures with genotype of carcinogen-metabolizing genes will be investigated with respect to the risk of breast cancer. Expression of p53 and erbB-2 in relation to organochlorine exposure and carcinogen-metabolizing genotype will be assessed. In addition, estrogen and progesterone receptor, p53, and BRCA1 haplotypes levels have been determined in some women. Statistical analyses will be designed to model cancer risk associated with environmental exposures and their interaction with genetic and biological markers.

Breast Cancer Risk Factors in Hispanic Women

Institution: Northern California Cancer Center
Study Start Date: August 1, 1995
Study End Date: May 31, 2000
Principal Investigator/Contact: Esther M. John, Ph.D.

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* Also funded by NIEHS.

Although Hispanic women in California have 50 percent lower incidence of breast cancer than non-Hispanic white women, breast cancer is the leading incident cancer in Hispanic women. Yet few published data on breast cancer risk factors in Hispanics are available, and analytic studies have not adequately explored the reasons for the differences in incidence rates between Hispanics and whites. The researchers are conducting a population-based case-control study in the San Francisco Bay area among Hispanic women to assess the associations of breast cancer with migration patterns and acculturation, and with potentially modifiable factors such as physical activity, vitamin D from sunlight exposure and diet, breastfeeding, and phytoestrogen intake.

Cases include all Hispanic women ages 35 to 79 years who were diagnosed with breast cancer between 1995 and 1998 and resided in the San Francisco Bay area at the time of diagnosis. Cases are ascertained through the population-based cancer registry of the Greater Bay area. Hispanic controls living in the San Francisco Bay area are identified through random-digit dialing and are frequency-matched to cases by 5-year age group in a ratio of 1.5 controls per case.

Professional bilingual and bicultural interviewers conduct home visits and administer a structured questionnaire and measure skin pigmentation and anthropometry (i.e., weight, height, and hip and waist circumferences). The interview collects information on demographic background, residential history, physical activity, sunlight exposure, diet, supplement use, body size, change in weight, occupational history, pregnancy and menstrual history, hormone use, and medical history. The researchers estimate that they will complete interviews and measurements for 506 cases and 759 controls by the summer of 1999.

Interview data and measurements from cases and controls will be compared to test the hypotheses that breast cancer risk is reduced among women with high physical activity, high vitamin D from sunlight exposure and diet, high phytoestrogen intake, long periods of breastfeeding, low level of acculturation, and recent migration to the United States. The researchers also will evaluate the association with risk factors that have been established in mostly white populations. Unconditional logistic regression will be used to estimate the odds ratios for breast cancer associated with the exposures of interest, controlling for age and potentially confounding variables. Researchers also will compare the prevalence of risk factors and magnitudes of associations in Hispanics with different migration patterns and levels of acculturation in order to elucidate the factors that contribute to the increase in breast cancer risk as Hispanic women migrate from low-risk to high-risk countries. The data analysis will be completed by May 2000.

Multiethnic/Minority Cohort Study of Diet and Cancer

Institution: University of Hawaii
Study Start Date: February 1993
Study End Date: February 2003
Principal Investigator/Contact: Laurence Kolonel, M.D., Ph.D.

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A large epidemiologic cohort was established in Hawaii and Los Angeles during the period of 1993 to 1996. The population-based cohort, composed of more than 215,000 members, is unique in its multiethnic composition, including substantial numbers of Latinos, African Americans, Japanese Americans, and whites. At entry, each participant completed a 26-page mail questionnaire that contained a quantitative diet history; medical, medication, physical activity, and female reproductive histories; and demographic information. In addition to maintaining a high rate of followup on the cohort, the researchers will study the relationship of several dietary factors to four common cancer sites: prostate, breast, colorectum, and lung. Associations of these cancers with nutrients (e.g., prostate cancer with saturated fat, lycopene; breast cancer with the ratio of monounsaturated to saturated/polyunsaturated fat, components of dietary fiber; colorectal cancer with fat, energy, folate; lung cancer with specific fats, carotenoids) and with foods (e.g., prostate cancer with red meat, legumes; breast cancer with high-fiber vegetables; colorectal cancer with meats cooked at high temperature, legumes; lung cancer with animal products, food sources of carotenoids) will be examined, taking advantage of both the diversity and range of intakes among cohort members. These relationships will first be examined within each ethnic group. Then, the consistency of relationships among the different ethnic groups will be evaluated, using calibrated dietary exposure values based on 24-hour dietary recall data collected on a large subsample of the cohort. Finally, the extent to which dietary and nondietary data can account for interethnic differences in cancer risk will be assessed. Passive followup on the cohort will use computer linkage to the population-based cancer registries in Hawaii and California and should yield at least 2,542 breast, 3,426 prostate, 2,737 colorectal, and 2,034 lung cancer incident cases by the year 2002. Active followup will include the administration of a brief followup questionnaire in the first 2 years of the renewal period, as well as regular mailings of a study newsletter. Findings from this study should help to elucidate the relationship of diet to cancer and to better understand the basis for ethnic variations in cancer incidence.

Defining Diet-Related Breast Cancer Risks in Black Women

Institution: University of Illinois at Chicago
Study Start Date: September 30, 1995
Study End Date: September 29, 1998
Principal Investigator/Contact: Shiriki Kumanyika, Ph.D.

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Breast cancer mortality is higher in black than in white women. The incidence of premenopausal breast cancer is higher in black than in white women and, in some age groups, is increasing at a faster rate than in white women. These and other aspects of breast cancer epidemiology suggest the need for within-race studies of the causes and prevention of breast cancer in black women. Dietary factors, as universal and potentially modifiable risk factors, are of substantial interest in this respect. Yet the contribution of diet to breast cancer etiology has been difficult to specify, partly due to methodological problems with dietary assessment. The proposed studies are motivated by evidence suggesting that effective implementation of the needed studies of diet in breast cancer etiology in black women is especially impeded by methodological problems: food frequency or dietary history methods that have acceptable validity in white populations appear to have less validity in black populations. These problems can be overcome, in part, by the application of certain statistical approaches to correct for measurement error—approaches requiring repeated-measures data collected from the same population with a more accurate method.

Studies are proposed to (1) assess the validity of food-frequency questionnaire data collected from a sample of black women and (2) quantify the impact of the associated error on epidemiologic analyses of diet and breast cancer risk. The researchers will use telephone and mail contacts to collect three unannounced 24-hour dietary recalls and one 3-day food record from a geographically dispersed sample of 400 black women. The women will be sampled from a large cohort of black women who completed a food-frequency questionnaire as part of their enrollment in a large cohort study. The recall and record data will constitute reference data approximating "true" intake and will support comprehensive statistical modeling to quantify random variation (i.e., intrapersonal differences in nutrient intakes from day to day) and bias (systematic departures of nutrient intakes estimated from the food-frequency questionnaire). Separate analyses will be done for each of several key nutrients of interest in relation to breast cancer etiology, including energy, total fat, saturated fat, dietary fiber, beta carotene, vitamin C, vitamin E, and alcohol. Deattenuation and correction factors derived from the dietary assessment studies will be used in exploratory analyses of dietary risk factors for incident breast cancer using data from the prospective study database. Thus, this research will yield statistical methods for enhancing the ability to assess diet-related breast cancer risks in black women as well as relevant pilot data to support future studies.

Health, Eating, Activity, and Lifestyle (HEAL) Study in Breast Cancer Prognosis Among Black, Hispanic, and Non-Hispanic White Women

Institution: University of New Mexico, PI—Richard Baumgartner, Ph.D.
Fred Hutchinson Cancer Research Center, PI—Anne McTiernan, M.D., Ph.D.
University of Southern California, PI—Leslie Bernstein, Ph.D., Frank D. Gilliland, M.D., Ph.D.
Study Start Date: Series of pilot studies initiated in 1996
Study End Date: Varies by study
Contact: Rachel Ballard-Barbash, M.D., M.P.H.

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In October 1996, NCI initiated support for a series of pilot and methods development studies to examine the association of weight, physical activity, diet, serum hormones, tumor characteristics, and breast cancer prognosis. The objectives of the study are:

- To determine prognostic factors for breast cancer that are modifiable by women, such as weight, physical activity, and diet, in a population-based cohort of women diagnosed with incident Stage 0-3a breast cancers.

- To determine the influence of these potentially modifiable factors on the following parameters related to breast cancer: (1) occurrence of invasive cancer among women with carcinoma in situ; (2) severity of cancer at diagnosis, including histologic diagnosis, grade, and stage; (3) occurrence of second primary and recurrent breast cancer; and (4) survival.

- To determine the cross-sectional and longitudinal relationships between body composition, diet, physical activity, and hormone profiles (estrogens, testosterone, sex hormone binding globulin, C-peptide, IGF-1, FSH, and leptin) in a population-based cohort of women with Stage 0-3a breast cancer.

- To determine the association of tumor-related prognostic factors with these measures and with other prognostic variables, such as tumor histology, grade, stage, and tumor expression of various markers, such as ER/PR, HER 2-neu, or p53.

Approximately 1,200 women from a mixture of ethnic backgrounds (non-Hispanic white, Hispanic, African American) are enrolled in the cohort from three sites across the United States (New Mexico, Seattle, and Los Angeles). The cohort will provide preliminary data on how best

to measure these prognostic factors in women with Stage 0-3a breast cancer. In addition, it will provide pilot data for identifying the most promising questions to pursue in developing a larger cohort of breast cancer patients for examining issues related to modifiable risk factors and prognosis.

SPORE in Breast Cancer

Institution: University of North Carolina at Chapel Hill
Study Start Date: August 1, 1992
Study End Date: July 31, 2000
Principal Investigator/Contact: H. Shelton Earp III, M.D.

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The goal of the University of North Carolina (UNC) SPORE is to reduce breast cancer mortality and incidence in North Carolina through an interdisciplinary program of research and intervention that (1) integrates efforts in cancer prevention and control, molecular epidemiology, clinical research, and laboratory sciences and (2) targets behavioral and biologic issues relevant to African American women. The six primary objectives of the UNC SPORE are to (1) identify the determinants of the gap in breast cancer mortality in North Carolina between African American and white women, and then to use novel community and provider interventions to increase early detection and eliminate the gap; (2) initiate a long-term, population-based study of breast cancer etiology in a defined North Carolina population containing 630,000 women ages 20 to 74, 29 percent of whom are African American; (3) combine molecular biology and epidemiology in the investigation of the environmental and genetic determinants of breast cancer in African American and white women in the defined population; (4) develop new clinical markers for neoplastic proliferation of breast cancer cells through the discovery of new genes; (5) promote new translational research projects and recruit new investigators to breast cancer research; and (6) complement the NCI and other SPOREs in the national effort to reduce breast cancer mortality and incidence by focusing on minority issues, development and use of novel molecular epidemiologic approaches, and the development of public health research programs in breast cancer control.

SPORE in Breast Cancer: The Carolina Breast Cancer Study

Institution: University of North Carolina at Chapel Hill
Study Start Date: September 1992
Study End Date: September 2000
Principal Investigator/Contact: Beth Newman, Ph.D.

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The Carolina Breast Cancer Study (CBCS) is a population-based case-control study that integrates molecular biology and epidemiology in the search for causes of breast cancer. Participants include 20- to 74-year-old women residing in a 24-county area of central and eastern North Carolina. Cases are women diagnosed with invasive or in situ breast cancer for the first time between May 1, 1993, and March 31, 2000. Comparison subjects are frequency-matched to cases by sex, race, and age (+/– 5 years) and are identified using computerized lists from the North Carolina Division of Motor Vehicles for women 20 to 64 years old and from the U.S. Health Care Financing Administration for women 65 to 74 years old. By the end of the funding cycle, data from 1,600 women with invasive breast cancer and an equal number of appropriate controls will be available. Sampling will ensure that approximately 50 percent of cases and controls are African American and 50 percent are younger than age 50. Information on established and hypothesized breast cancer risk factors is obtained by personal interview. Blood samples for extraction of germline DNA are collected from all consenting participants, and paraffin-embedded tumor specimens are requested for all breast cancer cases. Medical records are obtained to document treatment, stage, and prognostic characteristics to supplement descriptions available from pathology review of slides of the breast tumor. The epidemiologic and clinical data and biological specimens will provide the basic resources necessary to address the relative contributions of genes and environment to breast carcinogenesis.

The scientific questions of particular interest in this study are (1) to what extent inherited susceptibility at various loci (e.g., BRCA1, BRCA2, ATM, AR) contributes to breast cancer and which environmental/behavioral factors influence penetrance of the disease mutations; (2) whether specific, somatic, molecular alterations or other characteristics (e.g., amplification of HER-2/neu, PRAD1/EMS1, or c-MYC; p53 mutations/overexpressions; ER and PR status) can serve as signatures for etiologically distinct subsets of breast cancer, and, if so, which environmental/behavioral exposures increase risk of their occurrence; (3) whether specific alleles at P450 or other metabolic loci (e.g., NAT1 and NAT2, CYP17, COMT, GSTM1/GSTP1/GSTT1) modulate effects of environmental exposures on breast cancer risk; and (4) whether racial differences in breast cancer among African American and white women can be explained by specific molecular alterations or constellations of risk factors. Sociodemographic factors and hormonal risk factors also will be considered.

In addition, the CBCS is structured to facilitate implementation of other current and proposed projects, including studies examining the H-ras VNTR; carcinoma in situ; the role of pesticides, occupational cadmium exposure, and electromagnetic fields in breast carcinogenesis; and the development of a genetic testing protocol for BRCA1.

Several sets of findings have been published, and other analyses are under way. So far, most analyses indicate that the relationship between the risk factors under study and the development of breast cancer is essentially the same among African American and white women.

SPORE in Breast Cancer: Case-Control Study of Carcinoma in Situ

Institution: University of North Carolina at Chapel Hill
Study Start Date: 1996
Study End Date: 2001
Principal Investigator/Contact: Robert Millikan, Ph.D., D.V.M.

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This case-control study of carcinoma in situ of the breast is being conducted in parallel with the Carolina Breast Cancer Study (CBCS). Participants include women from the 24-county area of central and eastern North Carolina covered by the CBCS. Cases include all women with a first diagnosis of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) between September 9, 1995, and February 28, 2000, identified through the Central Cancer Registry rapid-ascertainment system developed for that study. Based upon preliminary data collected during 1993, researchers expect 450 cases within the accrual period. Comparison subjects (controls) consist of an equal number of women without a history of in situ (or invasive) breast disease, frequency-matched to cases based upon expected distributions by age (+/– 5 years) and race. Controls are identified using records from the Department of Motor Vehicles and the Health Care Financing Administration. Information on established and hypothesized risk factors for breast cancer is obtained by personal interview. Blood samples for extraction of germline DNA are obtained from consenting participants, and paraffin-embedded tumor specimens and medical records are requested for all cases.

The research objectives are (1) to identify risk factors for occurrence of DCIS and LCIS; (2) to determine whether differences in histologic appearance as well as immunohistochemical and molecular profiles of in situ lesions reflect differences in underlying etiology (i.e., exposure to specific risk factors for breast cancer); (3) to specifically evaluate the contributions of tobacco smoking and chlorinated hydrocarbon pesticides, as well as other exposures in which a study of precursor lesions is expected to have advantages over previous epidemiologic studies employing invasive breast cancer as the sole endpoint; (4) to compare cases of in situ carcinoma in African American to white women to determine whether the mutational spectrum, histologic characteristics, or results of other biologic assays suggest different (possibly more aggressive) forms of breast cancer in African American women; (5) and to determine whether mutations in BRCA1, BRCA2, and other loci of inherited susceptibility represent risk factors for occurrence of in situ carcinoma of the breast.

Genetic Differences in H-ras VNTR Between Races

Institution: University of North Carolina at Chapel Hill
Study Start Date: N/A
Study End Date: N/A
Principal Investigator/Contact: Kathy Conway Dorsey, Ph.D.

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This research is focused on the H-ras variable number of tandem repeats (VNTR), which is a repeated DNA region located downstream of the Hras-1 protooncogene. Some studies have found that rare length variants of this region are associated with an increased risk of breast cancer. In the researchers' recent studies, they found that rare H-ras alleles were significantly associated with breast cancer in African American women but not in white women, and this effect may be related to the allelic variation between these two populations. Because this study comprised a relatively small number of African American women, the researchers are further evaluating the association of rare H-ras alleles with breast cancer in African American women by screening a much larger number of subjects in the Carolina Breast Cancer Study, a population-based case-control study of breast cancer in North Carolina in which half the subjects are African American. In addition to these population studies, the researchers also are investigating the putative biological function of the H-ras VNTR and the possible mechanism(s) underlying the association of this region with cancer.

Genotype/Hormone Interactions in Breast Cancer Susceptibility

Institution: University of Pennsylvania, Rebbeck Lab
Study Start Date: September 1, 1998
Study End Date: August 30, 2003
Principal Investigator/Contact: Timothy Rebbeck, Ph.D.

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There is strong evidence that a combination of inherited genotypes and hormone exposures influence breast cancer risk. Furthermore, inherited genotypes involved in the metabolism of

steroid hormones also may modify a woman's risk of developing breast cancer. Knowledge about the interactions of these factors in breast cancer etiology may improve the ability to identify women at increased breast cancer risk. This knowledge, in turn, may be used to target women for breast cancer prevention or treatment strategies. The researchers propose a population-based case-control study that will directly address the complex, multifactorial etiology of breast cancer that involves the interaction of genotypes and hormonal risk factors. These hormonal factors include endogenous exposures measured by parity-related events and exogenous exposures to compounds such as estrogen replacement therapy. This study will address a number of specific hypotheses.

First, the researchers will evaluate whether candidate susceptibility genotypes are associated with breast cancer in a case-control analysis. Among the genes that will be studied are CYP1A1, CYP3A4, catechol-O-methyltransferase, and other genes involved in the metabolism of steroid hormones. Second, the researchers will evaluate whether genotypes and other reproductive risk factors interact in breast cancer etiology and whether knowledge of genotypes will improve their understanding of breast cancer etiology once hormonal risk factors (e.g., reproductive history, estrogen replacement therapy) are known. Third, they will evaluate whether the genetic and hormonal etiology of breast cancer differs by race. To address these hypotheses, the researchers will undertake a study in the Greater Delaware Valley using an existing network of hospitals to identify a population-based sample of cases and random-digit-dialed controls. The sample will consist of 1,200 white and 1,200 African American subjects. Risk factor information will be obtained from a telephone interview, a biosample containing DNA will be collected using a noninvasive cheek swab method, and pathology information will be collected using standardized medical record abstraction. Analyses will be undertaken to evaluate the roll of candidate genotypes and hormonal risk factors in breast cancer etiology by race. These analyses will allow the researchers to examine genotype by hormonal interactions in breast cancer etiology.

Activity of P450-1A2 and 3A4 and Breast Cancer Risk

Institution: University of South Carolina at Columbia
Study Start Date: September 30, 1998
Study End Date: August 31, 2000
Principal Investigator/Contact: Wei Zheng, M.D.

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Estrogens play an important role in the etiology of breast cancer. Cytochrome P450-1A2 (CYP1A2) and 3A4 (CYP3A4) are two of the major enzymes in estrogen hydroxylation, forming biologically distinct metabolites: 2-hydroxy estrogens and 16alpha-/4-hydroxy estrogens,

respectively. It is thus conceivable that the risk of breast cancer may differ among women with different activities of these enzymes. Preliminary results from the researchers' pilot study suggest that high CYP3A4 activity or low CYP1A2 activity may be related to a substantially elevated risk of breast cancer. To extend these novel findings to a full-scale study, the researchers propose to analyze urine samples collected from a subset (250 case-control pairs) of study participants recruited in the Shanghai Breast Cancer Study, an ongoing NCI-funded population-based case-control study among Chinese women in Shanghai (R01 CA64271). In addition to in-person interviews and collection of fasting morning blood and urine samples, in vivo urinary caffeine tests also will have been completed for these women by September 1998. The urine samples collected after caffeine intake will be assayed for caffeine metabolites to determine the activity of CYP1A2, and overnight urine samples will be assayed for cortisol metabolites to determine the activity of CYP3A4. Because the caffeine tests and overnight urine collections are conducted prior to any cancer therapy for the breast cancer cases, the potential influence of disease and its sequelae should be minimized. The enzyme activity data collected from this study will be analyzed jointly with data collected from the main study to evaluate the association of CYP1A2 and CYP3A4 activities with breast cancer risk.

BRCA1 and BRCA2 in African American and Latino Families

Institution: University of Southern California
Study Start Date: February 1, 1998
Study End Date: January 2003
Principal Investigator/Contact: Brian E. Henderson, M.D.

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While knowledge about the penetrance and attributable risks associated with BRCA1 and BRCA2 mutations is continuing to be refined, the potential impact of these genes in minority populations remains largely unknown. As examples from the Ashkenazi Jewish and Icelandic subpopulations have demonstrated, different ethnic groups are likely to have different spectrums of mutations and polymorphisms occurring in BRCA1 and BRCA2. The identification of germline mutations in cancer susceptibility genes such as BRCA1 and BRCA2 has opened up the possibility of identifying and characterizing high-risk families and individuals. However, at the present time, the broad spectrum of mutations, limited knowledge of the functional role of these genes, and incomplete information on gene penetrance and factors that affect expression of these genes (i.e., gene-gene and gene-environment interactions) severely limit the practical application of such knowledge in cancer prevention and counseling.

This study aims to utilize a large, multiethnic, population-based cohort that will provide greater heterogeneity of gene mutations, allele frequencies, and environmental exposures than would be available within any single ethnic group. To fully exploit this multiethnic resource, investigators are studying families affected with at least two cases of breast or ovarian cancer and are comparing affected and unaffected siblings within and across ethnic groups. Specifically, they are investigating the role of BRCA1, BRCA2, the cytochrome P450cl7alpha gene (CYP17), and the 17beta-hydroxysteroid dehydrogenase 1 gene (HSD17B1) among African American and Latino families with a history of breast and ovarian cancer and are evaluating possible gene-gene and gene-environment interactions in the etiology of breast cancer. The primary rationale for studying families is to increase substantially the efficiency with which the specific aims can be achieved. Focusing on sibships with a family history of breast cancer will increase the proportion of subjects who carry a mutation in BRCA1 or BRCA2. Consequently, this will substantially increase the power of the study to estimate main effects and interactions. Further, the family-based design offers the advantage of being able to determine the role of polymorphisms in metabolic genes involved in estrogen biosynthesis without underlying confounding that can be introduced from genetic heterogeneity.

Breast Cancer Risk Factors of Hispanic and Non-Hispanic White Women

Institution: University of Southern California
Study Start Date: 1991
Study End Date: N/A
Principal Investigator/Contact: Frank D. Gilliland, M.D., Ph.D.

University of Southern California
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Los Angeles, CA 90033
323-442-1309
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Dr. Gilliland is working on a population-based case-control study comparing the breast cancer risk factors of Hispanic and non-Hispanic white women in New Mexico. Analysis of reproductive risk factors has been completed, and those results have been published. He currently is studying other risk factors, such as obesity, education level, and diet.

Medication Use and Breast Cancer

Institution: Yale University School of Medicine
Study Start Date: July 1996
Study End Date: June 2001
Principal Investigator/Contact: Patricia G. Moorman, Ph.D.

Department of Epidemiology and Public Health
Yale University School of Medicine
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New Haven, CT 06520-8034
203-785-6392
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The objective of this study is to examine the role of several commonly used medications that may either increase the risk of breast cancer (e.g., hormones, antidepressants) or decrease the risk (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], anti-oxidants). These studies will utilize the infrastructure established for a large, population-based case-control study of breast cancer in North Carolina, the Carolina Breast Cancer Study (CBCS). The CBCS enrolled 800 cases and 800 controls by the end of its first phase in spring 1996, and an additional 1,600 participants will be recruited in its second phase. The study population will have approximately equal numbers of African American and white women, allowing an evaluation of potential racial differences in the association of these medications and breast cancer risk. Information on hormone use and anti-oxidant consumption currently is being collected as part of a comprehensive questionnaire on breast cancer risk factors. Questions to assess the use of NSAIDs and antidepressants will be developed and added to the questionnaire used in the second phase of the CBCS. Analyses of the data will focus on hypotheses derived from preliminary investigations, including animal studies (i.e., NSAIDs' protective effect, antidepressants' tumor promotion effect) or questions that have remained unanswered due to temporal considerations (i.e., the risk of peri- and postmenopausal breast cancer among women who used oral contraceptives early in their reproductive years, the risk among women who used both oral contraceptives and menopausal hormones). The investigation of the roles these medications play in the development of breast cancer is important for several reasons. Physicians and patients should know the potential adverse effects associated with a given therapy so they can make informed judgments of the benefits versus the risks. Because millions of women are prescribed hormones and antidepressants each year, even a model increase in risk could translate into a large number of breast cancers. For the medications with evidence suggestive of a protect effect, it is important.

6. NATIONAL INSTITUTES OF HEALTH/NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The Women's Health Initiative

Institution: NHLBI
Study Start Date: 1992
Study End Date: 2007
Principal Investigators/Contacts: Jacques Rossouw, M.D., Project Officer; Suzanne Hurd, Ph.D., Acting Director

Dr. Rossouw
Women's Health Initiative
National Heart, Lung, and Blood Institute
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301-402-2900

The Women's Health Initiative (WHI) is a national, 40-site study examining health outcomes for women. It includes three randomized placebo-control clinical trials to study breast cancer outcomes related to (1) hormone replacement therapy, (2) dietary intervention, and (3) calcium and vitamin D intake. Enrollment for the trials, which began in 1993, was completed in September 1998. The 68,000 subjects enrolled in this study are postmenopausal women between the ages of 50 and 79 years whose racial backgrounds reflect proportions found in the U.S. population: 18.5 percent of the sample are from minority groups (African American, Hispanic, American Indian, Asian American, and Pacific Islander). Epidemiologic data and blood samples were collected from the subjects. Followup contact, in the clinic and by phone, takes place two times a year and will continue through 2005. Analysis will be completed for each minority group. Another component of the WHI is an observational study (a cohort study) of 100,000 women that links epidemiologic data to future health outcomes. The results will be used to predict risk for disease.

7. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Ethnicity, Body Composition, Bone Density, and Breast Cancer

Institution: University of Arizona
Study Start Date: October 1997
Study End Date: September 2002
Principal Investigator/Contact: Zhao Chen, Ph.D., M.P.H.

University of Arizona
P.O. Box 245163
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520-318-7241 (fax)

Recently two studies reported a strong association between high bone mass and increased risk of breast cancer. These results may raise new questions in decisionmaking for hormone replacement therapy and suggest a potential use of bone mass as an indicator of lifetime estrogen exposure for assessing risk of breast cancer. Additional studies in different ethnic groups appear warranted, because there is significant ethnic variation in frequencies, distributions, and severity

levels of both osteoporosis and breast cancer. Given the fact that the bone mineral density is higher, but the rate of breast cancer is lower, in Hispanic older women compared with Anglo women, the Hispanic postmenopausal women would be a model to further evaluate the relationship between breast cancer and bone mass. To date, most knowledge of risk factors for osteoporosis and breast cancer is mainly based on results from Anglo women. It is critical to examine those risk factors in the Hispanic population in order to form specific prevention strategies for this population. The Women's Health Initiative (WHI) provides a unique opportunity to undertake nested case-control studies to further examine these issues in different ethnic groups. However, within the WHI, there will not be a sufficient number of breast cancer cases to form a nested case-control study in Hispanic women, both because the number of Hispanic women in the WHI bone mineral density (BMD) study cohorts is small (expected n=800) and because the breast cancer rate is lower in Hispanic women compared with Anglo women.

The proposed study is a case-control research design. The controls will be chosen from the Hispanic participants of the Arizona WHI observation study group. No additional data will be collected from the controls. The cases (n=140) will be postmenopausal Hispanic women in Arizona who are newly diagnosed with breast cancer (obtained through collaborative oncologists and surgeons). Measurements will include anthropometry, body composition, BMD, peripheral white blood cells, and WHI questionnaires. The relationship between BMD and breast cancer will be evaluated using logistic regression analysis.

8. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Women's CARE Study

Institution: NICHD
Study Start Date: 1988
Study End Date: December 1998
Principal Investigator/Contact: Robert Spirtas

Contraceptive and Reproductive Health Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 8B-07
Rockville, MD 20852
301-496-4925

The Women's Contraceptive and Reproductive Experiences (CARE) Study is a national, multisite case-control study examining the relationship between the risk of breast cancer and the use of oral contraceptives among women ages 35 to 64 years. The African American population was oversampled to ensure a significant number of African American subjects; the subjects for this study are 30 percent African American and 70 percent white. Data collection, which began in 1992 and will conclude this year, includes the use of standardized interviews and collection of

blood specimens (for future genetic analysis) from all cases and controls and samples of tumor specimens from cases at two sites. Data analysis has begun.

9. NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Environmental and Genetic Determinants of Breast Cancer

See listing under NCI.

10. NORTH CENTRAL CANCER TREATMENT GROUP

Breast Cancer Risk Factors and Mammographic Breast Density in American Indian and Alaska Native Women

Institution: Mayo Clinic Rochester
Study Start Date: July 1997
Study End Date: December 1999
Principal Investigators/Contacts: Judith Kaur, M.D., Marilyn Roubidoux

Dr. Kaur
Division of Medical Oncology
Mayo Medical School
Mayo Clinic
200 First Street, SW
Rochester, MN 55901
507-284-8318

Dr. Roubidoux
313-936-4367

Drs. Roubidoux (University of Michigan Medical Center) and Kaur (Mayo Clinic) collected data on personal risk factors of American Indian women and mammographic characteristics and determined that Sioux women have less dense breast tissue than women of other races but have similar rates of positive family history, abnormal mammograms, and detected malignancy. This result suggests that mammography may be a more sensitive screening tool in the detection of breast cancer in these women than in the general population. The data set now includes southwestern tribes and Alaska Native women.

Molecular Markers in American Indian and Alaska Native Women With Breast Cancer

Institution: Mayo Clinic Rochester
Study Start Date: July 1997
Study End Date: N/A
Principal Investigator/Contact: Judith Kaur, M.D.

Division of Medical Oncology
Mayo Medical School
Mayo Clinic
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Rochester, MN 55901
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This study will use archival tissues from patients diagnosed with breast cancer and will use immunohistochemical methods to assess 10 prognostic molecular factors. American Indian and Alaska Native women will be matched for age and stage with Caucasian women previously treated on North Central protocols.

11. SUSAN G. KOMEN BREAST CANCER FOUNDATION

Visceral Fat, BMD, and Breast Cancer: African Americans

Institution: Howard University Cancer Center
Study Start Date: January 1, 1997
Study End Date: September 30, 1998
Principal Investigator/Contact: Lucile L. Adams-Campbell, Ph.D.

Howard University Cancer Center
2041 Georgia Avenue, NW, Room 220
Washington, DC 20060
202-806-7697
202-667-1686 (fax)

This study is designed to examine the relationship between abdominal visceral fat, estrogen, bone mineral density, and breast cancer in pre- and postmenopausal African American women.

Establishing Tumor Tissue Banks and DNA and cDNA Gene Banks of African American Women With Breast Cancer

Institution: Howard University College of Medicine
Study Start Date: February 2, 1996
Study End Date: January 31, 1999
Principal Investigator/Contact: Indra Poola, Ph.D.

Departments of Pharmacology and Biochemistry and Molecular Biology
Howard University College of Medicine
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Washington, DC 20059
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Dr. Poola is evaluating fresh tissue DNA in a study of aggressive tumors in African American women with breast cancer. The specific aims of the project are to establish tumor tissue banks and DNA and cDNA gene banks of African American women with breast cancer and to evaluate the structural variability in the estrogen receptor gene. Dr. Poola obtained Institutional Review Board approval from Howard University Hospital, Providence Hospital, DC General Hospital, and Prince Georges Hospital Center and began collecting, labeling, and storing samples. Information recorded on each sample includes patient name, age, race, hormone receptor status, histological data (such as tumor size and grade), stage of diagnosis, date of biopsy, node positive or negative, metastatic status, date and place of birth, ethnicity, family history of cancer, occupation, cigarette use, and alcohol consumption. Reverse transcriptase polymerase chain reaction methodologies are used to evaluate the samples for the estrogen receptor gene. Although samples continue to be collected, many already have been analyzed; about 50 percent of the tumors studied have truncations in exon 1, and 60 percent have truncations in exon 8. Exons 1 and 8 represent the amino and carboxy terminal ends of the receptor. In addition, all of the analyzed tumors have deletions in exon 1, 2, 3, 5, and 7. Dr. Poola also has joined the NCI Cooperative Human Tissue Network and plans to share tumor tissue and DNA banks with other investigators.

Clinical and Genetic Screening of High-Risk African American Breast Cancer Families

Institution: Howard University Hospital
Study Start Date: January 1, 1997
Study End Date: December 31, 1999
Principal Investigator/Contact: Marlene H. McKetty, Ph.D.

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Goals of this study include increasing the number of high-risk women screened for breast cancer and augmenting the determination of a mutation profile and frequencies of known breast cancer susceptibility genes among high-risk women. The clinical screening component of the study, which has been completed for more than 300 subjects, is available to any African American woman with a family history of breast cancer in at least one primary or secondary degree relative. Included in the screening is a free breast examination, a mammogram, and breast cancer educational materials, including breast self-examination instructions. Women with abnormal mammograms and/or sonograms are routinely referred to a surgeon for evaluation, and—in some cases—biopsies are obtained. Genetic screening in a subset of 45 cases from high-risk breast cancer families revealed germline mutations in the coding and flanking intron regions of the BRCA1 gene. Eight different types of mutations have been identified; two are frame shift and six are missense. Screening the subset of cases from high-risk breast cancer families for BRCA2 is expected. Dr. McKetty is collaborating with Project WISH (Women Into Staying Healthy), a program of the District of Columbia's Department of Health. It is hoped that this collaboration

will increase the screens of high-risk women by as much as 30 percent. The collection of data and blood samples from the informative breast cancer families will continue.